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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/704,054	D'AMATO, ROBERT	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,27-29 and 73-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,27-29 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/12/2008, 2/12/2009, and 2/25/2009.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 12/12/2008, are acknowledged and entered. Claims 25-26, 31, 33-40, 59-62, and 71-72 have been cancelled by Applicant. Claims 73-76 are newly added. Claims 23, 27-29, and 73-76 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 25-26, 31, 33-40, 59-62, and 71-72 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 12/12/2008, 2/12/2009, and 2/25/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Specification

Applicant's amendment to the title of the application, filed 12/12/2008, is acknowledged and entered.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 23, 25-31, 33, 35-40, 59-62, and 71-72 as being indefinite regarding the term "blood-borne tumors" is **withdrawn** in light of the Dictionary definition of "borne". By definition, *borne* means "transported or transmitted by" (see attached Dictionary definition). As such, the claims broadly encompass the administration to any patient having a

tumor "transported or transmitted by" the blood, including secondary tumors resulting from the metastasis of a primary tumor as well as hematological malignancies such as leukemias.

Claim Rejections - 35 USC § 112 – 1st Paragraph – New Grounds of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. This is a new matter rejection.

Upon further consideration, recitation of "blood-*borne* tumors" in the claims is new matter not supported by the originally filed disclosure. This rejection is based on the Dictionary definition of "borne". By definition, *borne* means "transported or transmitted by" (see attached Dictionary definition).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

The originally filed specification discloses "...blood-*born* tumors such as leukemias..." (page 5, lines 20-21; page 9, line 19). Applicant's preliminary amendment filed 7/2/2001 recites "blood-*born* tumors" in claim 34. Applicant's amendment filed 3/19/2002 also recites "blood-*born* tumors" in claim 34, but in newly added claim 58 recites "blood-*borne* tumors". There is

no support for the claimed "blood-*borne* tumors" as added in claim 58 of the 3/19/2002 claim set and presently recited in the instant claims.

The words *born* and *borne* have completely different meanings. Whereas *born* means "deriving or resulting from" the word *borne* means "transported or transmitted by" (see attached Dictionary definitions). The originally filed specification discloses the use of thalidomide to treat "blood-born tumors" (*i.e.*, tumors deriving or resulting from blood such as leukemia) but not "blood-borne tumors" (*i.e.*, encompassing tumors transported or transmitted by blood such as secondary tumors resulting from the metastasis of a primary tumor).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 23, 27-29, and 73-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. This is a new matter rejection.

Upon further consideration, recitation of "therapeutically effective amount of thalidomide" in the claims is new matter not supported by the originally filed disclosure.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

The originally filed specification discloses the treatment of angiogenic related diseases and disorders comprising administering dosages "sufficient to inhibit angiogenesis" (page 8, lines 20-22) or "an effective amount of a teratogenic compound that is antiangiogenic" (page 12, lines 5-7). Applicants disclose oral dosages as recited in claims 27-29 and 74-76 at page 21,

lines 6-10. The originally filed claims recite administration of "...an angiogenesis inhibiting amount of thalidomide..." to inhibit tumor formation or growth in a human or animal. There is no support for the presently claimed "therapeutically effective amount of thalidomide " for treating blood-borne tumors.

No where in the originally filed disclosure is the phrase "therapeutically effective amount" recited. As such, Applicants lack explicit support for this claim limitation. With regard to implicit support, the entire disclosure is related to inhibition of angiogenesis and all administration methods and doses disclosed in the specification relate to amounts of active compounds sufficient to inhibit angiogenesis. As such, Applicants do not have support for the broadly claimed "therapeutically effective amount of thalidomide".

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 23 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating multiple myeloma, does not reasonably provide enablement for treating "blood-*borne* tumors". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to

> practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to treating blood-borne tumors in a patient comprising the administration of a therapeutically effective amount of thalidomide. As discussed *supra*, "blood-borne tumors" encompass tumors transported or transmitted by blood such as secondary tumors resulting from the metastasis of a primary tumor. The relative skill of those in the art is high,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art with respect to animal models of cancer, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431) (both of record).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

As illustrative of the state of the art with respect to administering thalidomide to inhibit tumor growth, the examiner cites Bach *et al.* (Acta Path., 1963, *59*:491-499) (cited by applicant), Gutman *et al.* (Anticancer Research, 1996, *16*:3673-3677), DiPaolo (Cancer Chemotherapy Reports, 1963, *29*:99-102) (cited by applicant), Thomas *et al.* (Current Opinion in Oncology,

2000, *12*:564-573) and Grabstald *et al.* (Clinical Pharmacology and Therapeutics, 1965, *6*:298-302) (cited by applicant). All references are cited for evidentiary purposes only.

Bach *et al.* studied the possible antineoplastic effect of thalidomide in experimental mouse models. The reference also discusses a report in which a woman with an X-ray resistant pelvic tumors was treated with thalidomide (400 mg daily). The tumors increased in size during the treatment. Bach *et al.* transplanted NJA tumors (a transplantable leukemia) and PBH tumors (an adenocarcinoma) in mice (page 494). The mice were then treated with varying doses (11.2, 112.0, 560.0 and 1120.0 mg/kg) of thalidomide (page 495). In mice with PBH tumors, all thalidomide treated mice died before controls (pages 496-497). In the NJA implanted mice, there was no significant effect of thalidomide on the survival times of the animals. Further, histological exam revealed no difference with regard to the extent of the leukemic infiltrations in the organs between treated and untreated mice (pages 496-497). The authors conclude that thalidomide had no antineoplastic effect (page 498).

Gutman *et al.* tested the efficacy of thalidomide in treating solid tumors in mice (Abstract). B16-F10 (melanoma) and CT-26 (colon carcinoma) cells were injected in mice and the mice then received 0.3-1.0 mg thalidomide (*id.*). There was no growth retardation in CT-26 bearing mice or in mice with pulmonary or peritoneal metastases of B16-F10 melanoma (*id.*). All tumors reached maximum size, similar to controls. Further, morphological exam revealed that in both thalidomide and control groups, all mice had developed an intact network of new blood vessels (*id.*). In conclusion, the authors report that the present study did not demonstrate a sustained, reproducible, anti-angiogenic effect of thalidomide in solid tumors growing in mice (page 3676).

DiPaolo also studied the effects of thalidomide in treating standard rat and mouse tumors, including adenocarcinoma, Ehrlich ascites, leukemia, sarcoma, Murphy-Sturm, lymphosarcoma and Walker 256 (Table 1). The daily dose of thalidomide was 500 mg/kg (*id.*). Based on the results of this study, DiPaolo concludes, "thalidomide is ineffective against transplantable cancers" (page 102).

Thus, in three separate studies, thalidomide was ineffective in inhibiting tumor growth in mouse models of cancer. Given this information, the skilled artisan would not reasonably expect thalidomide to be effective in treating tumors in humans.

Grabstald *et al.* is cited as evidence to support the unpredictability of treating tumors in humans using thalidomide. In fact, Applicant admits that Grabstald *et al.* teach away from the present invention (see Response filed January 27, 2005). The reference teaches that thalidomide was administered to 71 patients with a wide spectrum of cancers (Abstract). There was no evidence of an objective response in any cancer except one patient with renal cell cancer (*id.* at page 301). The authors conclude, "further random trials of this [thalidomide] drug against cancer in man are not indicated" (page 301). It is noted that Grabstald *et al.* would clearly render obvious the claimed invention if the reference provided some reasonable predictability or expectation of success.

Thomas *et al.* provides a review of the current role of thalidomide in cancer treatment. Although the article will not be discussed in detail, several points are pertinent to the present rejection. Firstly, the article states that the first oncology studies of thalidomide were reported in 1965 (Grabstald *et al.*, cited *supra*). Further, another study of 21 patients with various solid tumors who were treated with thalidomide revealed no tumor regressions (page 564). Secondly, several clinical trials of thalidomide have been carried out (pages 566-569). Thalidomide has shown moderate effects in some cancers (gliomas – 2/36 patients had partial response, 2/36 patients had a minor response, and 12/36 had stable disease; Kaposi's sarcoma – 6/17 patients had a partial response, 8/17 patients withdrew from toxicity; renal cell carcinoma – 3/18 patients had partial response) (pages 566-567). However, there were no objective tumor responses in 63 patients with metastatic prostate cancer, no objective responses in 17 patients with melanoma, no objective responses in 12 patients with breast cancer or 19 patients with ovarian carcinoma, and no objective tumor responses in 17 patients with metastatic squamous cell carcinoma of the head and neck (in fact, 94% of patients had progressive disease) (pages 567-568). Thirdly, a summary of FDA new drug applications issued for thalidomide between 1997 and 1998 yielded data on 480 patients treated for breast, CNS, prostate, skin, colon, pancreas and kidney malignancies. Thalidomide was given in doses up to 2400 mg daily. Responses were observed in 36 patients (7.5%), 10 of who had received combination therapy (*i.e.* not thalidomide alone), whereas 53% of patients discontinued therapy because of toxicity (page 568). Thus, it is clear that the treatment of tumors in humans with thalidomide is extremely unpredictable and in the majority of cases completely ineffective.

Applicants own admissions on the record provide further evidence that the treatment of tumors in humans with thalidomide is entirely unpredictable. For example, in Applicant's response filed 8/7/2006, applicant submitted that 19 references "indicate that thalidomide was not successful in inhibiting tumors in animals and humans" (page 16 of response filed 8/7/2006). Further, Applicant states (emphasis added), "Moreover, Applicant respectfully points out that several references actually teach that **thalidomide has cancer-promoting or carcinogenic activity**" (*id.*). Further still, Applicant states (emphasis added), "The references disclose **not only failure** but the **complete opposite effect** to the claimed invention" (*id.*). Applicant goes on to cite several studies wherein thalidomide was administered to humans with various tumors. Applicant concludes (emphasis added), "Again, **all of these studies failed to provide any promise for thalidomide as effective in inhibiting the formation or growth of tumors in humans**. The studies neither provide with any suggestion, **nor a reasonable expectation of success in inhibiting tumors in humans**" (*id.* at page 17). Thus, it is clear that thalidomide may actually promote cancer in some instances and in fact may have the opposite effect to that instantly claimed.

Thus, a preponderance of evidence suggests that treating tumors with thalidomide, particularly in humans, is extremely unpredictable and in most cases ineffective. Further, it is evident that thalidomide may actually have the complete opposite effect than those instantly.

2. The breadth of the claims

The claims are broad insofar as they recite the treatment of any "blood-*borne* tumor" by administering a "therapeutically effective amount" of thalidomide. As evidenced by the references cited *supra*, most human cancers and tumors are **not** sensitive to thalidomide treatment.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The working examples are limited to

demonstrating the anti-angiogenic activity of thalidomide in animal models of angiogenesis. While angiogenesis is one factor involved in tumor growth, there are many other factors that influence tumor growth. As such, the fact that thalidomide inhibits angiogenesis does not reasonably suggest that it will be effective in inhibiting tumor growth. In fact, as discussed *supra*, the prior art supports the idea that thalidomide is ineffective in inhibiting tumor growth in humans and therefore supports the Examiner's position that the working examples do not correlate to inhibition of tumor growth. Thus, the Applicant at best has provided specific direction or guidance only for the inhibition of angiogenesis with thalidomide. Although broad doses and administration routes of thalidomide are described in the specification, these doses and administration routes are contemplated to be useful for the treatment of any all angiogenic-related conditions. No reasonably specific guidance is provided concerning useful therapeutic protocols for any specific conditions or diseases, particularly the treatment of tumors.

Further, there are no *in vitro* or *in vivo* experimental models of any diseases described, including cell proliferation or animal tumor models. While the administration routes disclosed in the specification are standard routes of administration for therapeutic agents, Applicant has provided no specific administration regimens (*e.g.* timing, specific doses, etc.) necessary to prevent, inhibit the growth of or inhibit metastases of any specific tumors. Finally, while Applicant recites a broad dose range (0.1 to 300 mg/kg/day), this dose range is not reasonably specific enough so as to provide adequate guidance to the skilled artisan in the treatment of "blood-borne tumors", especially considering that doses within this range have previously been administered to inhibit tumor growth or treat cancer and were entirely ineffective.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that thalidomide could be predictably used to prevent all tumors, inhibit the growth of all tumors and/or inhibit the metastasis of all tumors sensitive to thalidomide as inferred in the claims and contemplated by the specification. A preponderance of the evidence suggests that thalidomide is ineffective in treating tumors in humans.

Applicants have previously submitted post-filing art alleged to demonstrate that the specification and claims are enabled. The Examiner has carefully reviewed the cited post-filing art but is not convinced that such post-filing art negates the present rejection. It is not clear how the same compound can be administered to patients having the same condition (*e.g.*, a solid tumor or leukemia) and on one hand not be effective (prior art) and on another have efficacy (post-filing art). It is very clear from the prior art that thalidomide was ineffective as an anticancer agent. However, it is also apparent from post-filing art that thalidomide has been found to have moderate efficacy when administered in certain doses to certain patient populations. The determination of such doses and patients is not predictable based on the prior art of record. Applicant alleges that thalidomide can be used to treat "solid tumors" and "blood-born tumors" and now claims the treatment of "blood-*borne* tumors". However, in light of the fact that Applicant provides limited guidance or direction with respect to doses, administration schedules, etc. that would be expected to have efficacy in the treatment of "blood-*borne* tumors", the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 23, 25-31, 33, 35-40, and 71-72 as being anticipated by Grabstald *et al.* is **withdrawn** in light of Applicant's amendments and arguments.

The rejection of claims 23, 25-31, and 71-72 as being anticipated by Chen *et al.* is **withdrawn** in light of Applicant's amendments and arguments.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 59-62 as being unpatentable over Grabstald *et al.* or Chen *et al.* in view of Kaplan *et al.* is **withdrawn** in light of Applicant's amendments and arguments.

Claims 23, 27-29, and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Vogelsang *et al.*** (N. Engl. J. Med., 1992, vol. 326, pages 1055-1058) (Reference C304 in IDS filed 11/7/2007) in view of **Kaplan** (USP No. 5,385,901).

Vogelsang *et al.* disclose administration of thalidomide to patients with chronic graft versus host disease whose primary diagnosis was chronic myelogenous leukemia (21 patients) (Table 1). The reference thus teaches administration to patients "having the blood-borne tumors" as recited in claims 23 and 27-29 and to patients having "leukemia" as recited in claims 73-76.

Thalidomide was administered in an initial dose of 200 mg four times a day in adults (800 mg/day) and 3 mg per kg of body weight given four times a day in children (12 mg/kg/day) (page 1056, left column). These doses are "therapeutically effective amounts" as recited in the instant claims and obviate the doses recited in claims 27-29 and 74-76. For example, 800 mg/day administered to an average human adult is approximately 10 mg/kg/day.

Thalidomide was found to be "safe and effective" for the treatment of chronic graft-versus-host-disease (Abstract).

Vogelsang *et al.* do not explicitly disclose in what form thalidomide was administered (*e.g.*, capsule, tablet, powder, solution, etc.).

However, Kaplan discloses compounds useful for controlling abnormal concentrations of TNF-a in patients (Abstract). The compounds of the invention include thalidomide (Figures and Examples; Claims). With regard to administration routes and forms, Kaplan *et al.* teach that the

compounds of the invention can be administered orally in form of tablets, pills, lozenges, dragees and similar shaped and/or compressed preparations (col. 10, line 61 to col. 11, line 33).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to administer thalidomide to chronic myelogenous leukemia patients having graft-versus-host-disease *via* any administration known to be useful for such compounds. In this regard, Kaplan *et al.* teach and motivate one skilled in the art to administer compounds such as thalidomide *via* well known administration routes. As such, one skilled in the art would have been imbued with at least a reasonable expectation of success in formulating a dosage form of thalidomide for administration to chronic myelogenous leukemia patients having graft-versus-host-disease via the routes and in the dosage form instantly claimed with a reasonable expectation that such administration would be effective to treat graft-versus-host-disease in such patients as evidenced by Vogelsang *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614